UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,623	05/02/2001	Thomas Dyrberg	4401.214-US	6709

23650 7590 12/16/2004

NOVO NORDISK, INC.
PATENT DEPARTMENT
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER	
CELSA, BENNETT M	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

file 007

Advisory Action	Application No.	Applicant(s)	
	09/847,623	DYRBERG ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 October 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attachment.*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *6,8 and 9*.

   Claim(s) withdrawn from consideration: *11*.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *see attachment*

Bennett Celsa
Primary Examiner
Art Unit: 1639

Advisory Action (Cont.)

Outstanding Objection (s) and/or Rejection (s)

Claims 6, 8 and 9 are rejected under 35 U.S.C. 103 as obvious over Drejer et al. Diabetes Vol. 40 (Nov. 1991) pages 1488-1495 in view of the specification (pages 9-11 and Table 1 to demonstrate inherent properties alone or further in view of Bakaysa et al. US 5,474,978 (12/95:filed 6/94), DeFilippis US 5,461,031 (10/95: filed 6/94) and/or Balschmidt WO 95/00550 (1/95).

The presently claimed invention is drawn to a "pharmaceutical composition" comprising:

I. AspB25 human insulin which is

a. asserted to be a hormonally inactive insulin analogue (<7% of human insulin's activity in an in vitro fat cell or receptor binding assay);

b. "for treating or ameliorating type I diabetes" (intended use); and

c. "in an amount effective for said treating or ameliorating (type I diabetes)" AND

II. a pharmaceutically acceptable carrier or excipient.

The Drejer et al. reference teaches the *in vitro* screening of 5 (five) human insulin analogs, including Asp B25 human insulin and Asp B28 human insulin with the aim being: "to characterize five very different insulin analogues regarding their interaction with the insulin receptor in terms of binding affinity; kinetic properties, and ability to activate tyrosine kinase" which is a "prerequisite for investigations of the **in vivo activity of fast-acting analogues**" (e.g. see page 1488, especially right column: emphasis provided). Drejer et al. further concludes that "[T] he availability of analogues

with a broad range of receptor affinities may enable us to reach a better understanding of the mechanism of insulin action" but "**[I] n particular, analogues with very low and very high affinity will continue to be valuable for in vitro and in vivo studies**" (see page 1494: bottom left column to top right column: emphasis provided).

The Drejer et al. reference clearly teaches compositions comprising an Asp B25 human insulin compound which inherently is a hormonally inactive insulin analogue (<7% of human insulin's activity in an in vitro fat cell or receptor binding assay) as demonstrated by applicant's own specification teaching that AspB25 possesses such characteristics. See e.g. specification pages 9-11 and Table 1.

To the extent that the presently claimed invention is drawn to a composition, intended use limitations (e.g. for treating or ameliorating type I diabetes) is not afforded patentable weight.

Turning to the new claim limitation requiring the presence of AspB25 "in an amount effective for said treating or ameliorating (type I diabetes)" it is noted that the specification on pages 14-16 (and examples) indicate pharmaceutical compositions "prepared by conventional techniques" for broad administration (e.g. orally/parenterally/transdermally) of analogs alone or in pH buffered solution (e.g. with water, isotonic agents, preservative, auxiliary agents) without any indication of criticality regarding "effective amounts". The specification seems to indicate the non-criticality of analog amount which is effective to treat/ameliorate type 1 diabetes since no concentration amounts (or ranges) for various administration modes are disclosed.

In this regard, the Drejer et al. reference provides explicit motivation (as outlined above e.g. abstract; pages 1488 and 1494) for one of ordinary skill in the art utilizing conventional techniques to formulate pharmaceutical compositions comprising the Drejer insulin analogs, including Asp B25, in light of their expected value in *in vivo* studies, utilizing various amounts corresponding to various modes of administration (e.g. oral/parenteral/transdermal), especially for investigations involving the determination of these analogs for their **in vivo activity as fast-acting analogues** (emphasis provided).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to formulate pharmaceutical compositions comprising the Drejer insulin analogs, including Asp B25 in amounts within the scope of the presently claimed invention (e.g. "in an amount effective for said treating or ameliorating (type I diabetes)") in view of the non-criticality of the analog amount which is effective to treat/ameliorate type 1 diabetes.

Additionally, the prior art reference(s) need only to render obvious the claimed composition and it is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. In re Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991); MPEP 2144.

The Bakaysa et al. US 5,474,978 (12/95:filed 6/94), DeFilippis US 5,461,031 (10/95: filed 6/94) and/or Balschmidt WO 95/00550 (1/95) are all cited to demonstrate the making of pharmaceutical composition comprising fast-acting insulin analog Asp

B28 disclosed in the Drejer reference in amounts and modes of administration within the scope of the presently claimed invention; including Asp B28 insulin analog in pH buffered solution (e.g. with water, iosotonic agents, preservative, auxiliary agents) as disclosed in the present specification (e.g. see specification pages 14-16 and examples).

Accordingly, the Bakaysa, DeFilippis and/or Balschmidt references taken separately or in combination provide an illustration of the conventional means of formulating pharmaceutical compositions comprising the Drejer insulin analogs including AspB28 which is extrapolatable to AspB25 insulin analog. It is also noted that these references provide further motivation to formulate pharmaceutical compositions comprising Asp B25 in light of the Drejer reference teaching the capability of both AspB25 and Asp B28 being fast-acting insulin analogs and with the Bakaysa/DeFilippis/Balschmidt teaching of making/testing Asp B28 for its fast action and long duration.

Thus, it would have been prima facie obvious to one of ordinary skill in the art, further in view of the Bakaysa, DeFilippis and/or Balschmidt reference, to make pharmaceutical compositions comprising the Drejer insulin analogs, including AspB25, in amounts (an amount effective for said treating or ameliorating (type I diabetes)) within the scope of the presently claimed invention.

Discussion

Applicant's after-final arguments and amendment were considered but deemed nonpersuasive for the following reasons. Initially, it is noted that the above rejection was modified in respsonse to applicant's entered after-final amendment.

Applicant first argues that the present invention is based on the finding that administration of *hormonally inactive* insulin analogues is effective in preventing the onset of autoimmune diabetes; which was not taught by Drejer. In this regard, applicant asserts that the Examiner's emphasis on the reference teaching regarding Asp-B25 being a fast-acting insulin analogue is misplaced since *the present invention* (emphasis provided) does not encompass the use of fast-acting insulin analogs to treat hyperglycemia. This argument is not persuasive for the following reasons.

First, as pointed out in the rejection above, intended use limitations (e.g. "for treating or ameliorating type 1 diabetes") in **composition** claims are not afforded patentable weight. Applicant's claim is directed to a composition claim and NOT a method of use claim.

Secondly, and as additionally pointed out in the above rejection, it is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See MPEP 2144; In re Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991). In this regard, as pointed out in the Final Rejection, the Drejer reference, provided ample motivation to make pharmaceutical compositions. In this regard, the Drejer reference in various portions (e.g. abstract;

pages 1488 and 1494 etc.) clearly teaches the expected in vivo activity (e.g. as fast-acting insulin analogs) of the Drejer reference insulin analogs. Additionally, the in vivo utility of the AspB28 Drejer analog confirmed by the Bakaysa/DeFilippis/Balschmidt references provides further motivation to make pharmaceutical compositions comprising the Drejer AspB25 insulin analog in amounts within the scope of the presently claimed invention.

Applicant additionally argues that one of ordinary skill in the art would not be motivated to make pharmaceutical compositions of Asp-B25 compounds disclosed in the reference since the specification table teaches that this analogue is hormonally inactive and thus teaches away from the use of these analogues to treat hyperglycemia.

Initially, the specification table referred to in the rejection was cited in the rejection above strictly to demonstrate an "inherent" property met by the reference compound.

Secondly, an inherent property, unknown to the skilled artisan would not act to discourage one of ordinary skill in making pharmaceutical compositions comprising the compound.

Thirdly, as pointed out in the rejection above the Drejer reference provides ample motivation to make pharmaceutical compositions which could then be tested for their prospective pharmaceutical utility.

Finally, the secondary references provide additional motivation to make pharmaceutical compositions comprising the Drejer reference compound.

Applicant's arguments regarding the disclosure by the secondary references of "fast-acting" insulin analogues does not obviate the motivation of one of ordinary skill in the art to make pharmaceutical compositions comprising the Drejer reference compounds for intended use in treating diabetes. This is true regardless of the temporal nature of their (e.g. the reference compound's) bioactivity (e.g. fast-acting, slow acting or otherwise).

Accordingly, the above obviousness rejection is hereby maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
December 9, 2004